(d) polyoxyl 35 castor oil in an amount of from about 2.5 to about 10 weight % of the composition.

20. (once amended) A pharmaceutical composition comprising:

(a) a combination of solubilized (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) in an amount of about 3.9 weight % of the composition and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in an amount of about 15.6 weight % of the composition;

(b) a pharmaceutically acceptable organic solvent which comprises (1) oleic acid in an amount of about 70 weight % of the composition; and (2) propylene glycol in an amount of about 7.5 weight % of the composition;

(c) water in an amount of about 0.5 weight % of the composition; and

(d) polyoxyl 35 castor oil in an amount of about 2.5 weight % of the composition.

## REMARKS

This is a response to the Office Action dated August 9, 2002, the period for response to which has been extended from November 9, 2002 to February 9, 2003.

### Claims 1, 3-11, 14-21 are rejected under 35 U.S.C. 112, 1st paragraph

The Examiner has rejected claims 1, 3-11 and 14-21 under 35 U.S.C. 112, 1st paragraph. The Examiner contends that said claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

### I. Examiner contends that ritonavir is not useful or effective in treating AIDS patients, especially when given in the absence of other antiviral drugs.

The Examiner contends that the term "pharmaceutical composition" implies an assertion of therapeutic efficacy, but that no such efficacy is in evidence. The Examiner further argues that "a therapeutically effective drug is one which will provide a perceptible improvement in the condition of a patient who is afflicted with AIDS, and is exhibiting clear signs of immunosuppression," and that "there is no evidence that this is the case."

The Examiner requests Applicants to provide some evidence that ritonavir is effective to treat AIDS patients, especially when given in the absence of other antiviral drugs.

Applicants respectfully turn the Examiner's attention to MPEP Section 2107.03 (IV) wherein it is stated that "Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for Phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility."

In this case, Applicant not only initiated human clinical trials, but received approval from the Food and Drug Administration (FDA) for ritonavir for the treatment of HIV-infection. The NORVIR package insert states that "NORVIR is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on the results from a study in patients with advanced HIV disease that showed a reduction in both mortality and AIDS-defining clinical events for patients who received NORVIR **either alone** or in combination with nucleoside analogues." (emphasis added). Moreover, the 2003 PDR states that "the activity of NORVIR as **monotherapy** or in combination with nucleoside analogues has been evaluated in 1446 patients enrolled in two double-blind, randomized trials."

Therefore, Examiner should presume that Applicants have established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

**II. Examiner contends that ingredients other than ritonavir in claimed formulation will negatively alter bioavailability of ritonavir by causing a**

**substantial decrease in efficacy of ritonavir rendering it useless in the treatment of HIV infection.**

A "35 U.S.C. 112, 1st paragraph, rejection should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under 35 U.S.C. 101. In other words, Office personnel should not impose a "lack of utility" basis unless a 35 U.S.C. 101 rejection is proper. In particular, the factual showing needed to impose a rejection under 35 U.S.C. 101 must be provided if a rejection under 35 U.S.C. 112, 1st paragraph, is to be imposed on "lack of utility" grounds." See MPEP Section 2107.01 (IV).

Applicants respectfully turn Examiner's attention to MPEP Section 2107.02 (IV) wherein it is stated, in part, that, "to properly reject a claimed invention under 35 U.S.C. 101, the Office must (A) make a *prima facie* showing that the claimed invention lack utility, and (B) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. Accordingly, the PTO must do more than merely question operability – it must set forth factual reasons which would lead one skilled in the art to question the objective truth of the statement of operability. If the Office cannot develop a proper *prima facie* case and provide evidentiary support for a rejection under 35 U.S.C. 101, a rejection on this ground should not be imposed. The examiner bears the initial burden, on review of the prior art or on any other ground, or presenting a *prima facie* case of unpatentability.

In this case, the Examiner questions the efficacy of Applicants formulation yet provides no evidence which would lead a person having ordinary skill in the art of formulation to doubt the claimed formulation's efficacy. Further, the Examiner then rejects Applicants' claims based on his own questioning. The Office has not developed a proper *prima facie* case and has not provided evidentiary support for a rejection under 35 U.S.C. 101. Therefore, a rejection on this ground should not be imposed. The factual showing needed to impose a rejection under 35 U.S.C. 101 has not been provided, so a rejection under 35 U.S.C. 112, 1st paragraph, can not be imposed on "lack of utility" grounds.

For the following reasons, Applicants respectfully request the Examiner to withdraw the rejection of claims 1, 3-11 and 14-21 and allow same.

**Claims 1, 3-11 and 14-21 are rejected under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claims 1, 3-11 and 14-21 are rejected under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner argues that in Claim 1 the phrase "the total solution" occurs several times, and in each case lacks antecedent basis. Claim 1 has been amended to overcome this rejection. Applicants state that claim 1 is now in condition for allowance, and respectfully request the Examiner to allow same.

Next, the Examiner notes that in claim 10 the last compound listed has seven left hand brackets ("[") and five right hand brackets ("]"). In fact, there are seven left hand brackets ("[") and six right hand brackets ("]"). One of the right hand brackets was inadvertently replaced by a ")". Also, a hyphen was inadvertently left out between the number "2" and the word "quinolinylcarbonyl". Applicants have amended claim 10 to correct this inadvertent typographical error.

Applicants have also amended the claims so that when the terms "ritonavir", "indinavir", "saquinavir", "nelfinavir" and "tipranavir" are used they are accompanied by a structural representation per the Examiner's request.

The Examiner also argues that most of the claims recite the term "about" in reference to a range which renders the claims indefinite as to the upper and lower limits.

Applicants respectfully turn the Examiner's attention to MPEP Section 2173.05(b) wherein it states, for example, that the term "about" was used to define the area of the lower end of a mold as between 25 to about 45 % of the mold entrance and was held to be clear, but flexible. *Ex parte Eastwood*, 163 USPQ 316 (Bd. App. 1968). Similarly, in this case Applicants' use of the term "about" in its claims should be held as clearly defining the range but having some flexibility.

Next, the Examiner argues that claim 1 recites weight percentages which at the lower end constitute only 42.4 % of the total mixture. The Examiner then goes on to state that the claim mandates the presence of at least one other component that constitutes 57.6 % of the total

composition which the Examiner has labeled "mystery component". The Examiner then goes on to note that this "mystery component" renders the claim indefinite. Applicants would like to state that the term "mystery component" has been read in by the Examiner. Also, Applicants respectfully turn the Examiner's attention to MPEP Section 2111.03 wherein it is stated, in part, that "the transitional phrases "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. "Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim. "Comprising" leaves the claim open for the inclusion of unspecified ingredients even in major amounts." In this case, Applicants have done just that, the transitional phrase used in claim 1 is "comprising" and in Examiner's hypothetical of a composition having 57.6 % of unrecited element(s) is consistent with the MPEP's definition of clearly defined and allowable subject matter even when the unrecited element is in a major amount as in Examiner's hypothetical composition.

As to Examiner's question of adding up all the components to give 143 % it should be understood that ranges have been given for each component, and that the amounts of each component when selected from those ranges would create the composition. It is quite obvious that all of the components of a given composition can only add up to 100 %.

Applicants have amended claims 1, 3-11 and 14-21 by incorporating many of the Examiner's suggestion, and believe that the claims are now in comdition for allowance. Therefore, Applicants respectfully request the Examiner to withdraw the rejection of claims 1, 3-11 and 14-21 and allow same.

**Claims 1, 3-11 and 14-21 are rejected under 35 U.S.C. §103 as being unpatentable over Sham (WO 97/21685) in view of Yamamoto (U.S. Patent No. 5,264,223) or Yamamoto (U.S. Patent No. 5,756,123).**

Claims 1, 3-11 and 14-21 are rejected under 35 U.S.C. §103 as being unpatentable over WO 97/21685 (the Sham reference) in view of U.S. Patent Nos. 5,264,223 (the '223 patent) or 5,756,123 (the '123 patent).

The Examiner argues that the Sham reference discloses the invention substantially as claimed, except for the presence of water. The Examiner also argues that the '223 patent discloses capsules in which the water content is about 5 %, and the '123 patent discloses capsules in which the water content is in the range of 1-6 %. The Examiner, however, concedes that the '223 and '123 patents do not discloses the claimed compositions.

The Examiner notes that in the instant claim, it is recited that the quantity of water is in the range of about 0.4 to about 3.5 %. However, the Examiner argues that there is no requirement that a solution of the present invention contains water, and tha the claims encompass the possibility of a completely anhydrous composition being contained within a capsule that contains a small quantity of water such that the overall composition, including the capsule, contains about 0.4 to about 3.5 % water. The Examiner goes on to argue that it is to this embodiment a rejection is targeted.

The present invention requires water in an amount of from about 0.4 to about 3.5 weight % of the composition. This composition can then be encapsulated into a hard gelatin capsule or a soft gelatin capsule as claimed in claim 5. If claim 1 include the gelatin capsule as part of its claims, then why would dependent claim such as claim 5 be added. It would be redundant to say that an encapsulated composition can be encapsulated.

Obviously, claim 1 is directed to a composition containing, among other things, water in an amount of from about 0.4 to about 3.5 weight % of the composition. This composition is then encapsulated. There is no possibility of the composition being anhydrous, it requires water in an amount of from about 0.4 to about 3.5 weight % of the composition. This composition containing water is then encapsulated. Therefore, the embodiment that Examiner has targeted with a rejection does not exist.

Furthermore, Applicants remind the Examiner that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) (Claims were directed to an apparatus for producing an aerated cementitious composition by drawing air into the cementitious composition by driving the output pump at a capacity greater than the feed rate. The prior art reference taught that the feed means can be run at a variable speed, however the court found that this does not require that the output pump be run at the claimed speed so that air is drawn into the mixing chamber and is entrained in the

ingredients during operation. Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432.). See also *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992) (flexible landscape edging device which is conformable to a ground surface of varying slope not suggested by combination of prior art references).

A statement that modifications of the prior art to meet the claimed invention would have been " 'well within the ordinary skill of the art at the time the claimed invention was made' " because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000) (Court reversed obviousness rejection involving technologically simple concept because there was no finding as to the principle or specific understanding within the knowledge of a skilled artisan that would have motivated the skilled artisan to make the claimed invention); Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999) (The level of skill in the art cannot be relied upon to provide the suggestion to combine references.).

Therefore, in light of the foregoing comments, Applicants respectfully request the Examiner to withdraw the rejection of claims 1, 3-11 and 14-21 under 35 U.S.C. §103 as being unpatentable over the Sham reference in view of the '223 patent or the '123 patent, and allow same.

**Claims 1, 3-11 and 14-21 are rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 5,948,436 issued to Al-Razzak et al.**

Claims 1, 3-11 and 14-21 are rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 5,948,436 (the '436 patent) issued to Al-Razzak et al.

The Examiner argues that Al-Razzak et al. teaches the elements of the claimed invention. The Examiner then notes that Applicants have stated that the disclosed compositions do not contain fatty acids, and contends that while the disclosed compositions do not contain free fatty

acids, they contain fatty acids nonetheless and points to Col. 6, lines 50+. This is simply not the case.

What the Examiner points to in Col. 6, lines 50+ is a component named Gelucire® which is indeed not a fatty acid. Gelucire® is synthesized by an alcoholysis/esterification reaction using hydrogenated palm oil and PEG 1500 as starting materials. Gelucire® is therefore a well defined mixture of mono-,di-and triglycerides and mono-and di-**fatty acid esters** of polyethylene glycol. Therefore, the compositions disclosed in the '436 patent do not contain fatty acids.

The Examiner's deconstruction or cleavage of Gelucire® and, more particulalry, the mono-, di- and triglycerides as well as the mono- and di-fatty acid esters, into their subcomponents cannot stand. In this same manner, one could deconstruct any invention to its basic components, and use those components to base rejections. For example, one could then argue no carbon containing compounds should be patentable over another because they both contain carbon atoms.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In this case, none of the basic criteria have been met to establish a *prima facie* case of obviousness. Therefore, Applicants respectfully request the Examiner to withdraw rejections of claim 1, 3-11 and 14-21, and allow same.

## CONCLUSION

Applicants maintain that the claims are now in condition for allowance, and respectfully request the Examiner to allow same. Support for the amendments can be found throughout the specification. In order to advance the prosecution of this case, Applicants have incorporated many of the Examiner's suggestions into the newly amended claims, and invite the Examiner to a teleconference to resolve any other issues which the Examiner may have.

A three month extension is deemed necessary by the Applicants. Therefore, Applicants hereby expressly authorize the Commissioner to charge the appropriate fee of $930.00 (or other amount as required) to Deposit Account No. 01-0025.

Respectfully submitted,
Alani, et al.

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**MARKED UP VERSION OF THE CLAIMS AS AMENDED**

1. (twice amended) A pharmaceutical composition comprising:

(e) solubilized (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) or a combination of solubilized (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) and another HIV protease inhibiting compound, or pharmaceutically acceptable salts thereof, in an [the] amount of from about 1 [%] to about 50 [% by] weight % of the composition [of the total solution];

(f) a pharmaceutically acceptable organic solvent which comprises a medium and/or long chain fatty acid or a mixture thereof in an [the] amount of from about 40 [%] to about 75 [% by] weight % of the composition [of the total solution], and ethanol or propylene glycol in an [the] amount of from about 1 [%] to about 15 [% by] weight % of the composition [of the total solution];

(g) water in an [the] amount of from about 0.4 [%] to about 3.5 [% by] weight % of the composition [of the total solution]; and

(h) optionally, a pharmaceutically acceptable surfactant.

4. (twice amended) The composition according to Claim 1 comprising (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) or a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) and another HIV protease inhibiting compound selected from the group consisting of:

(2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane;

N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ( indinavir );

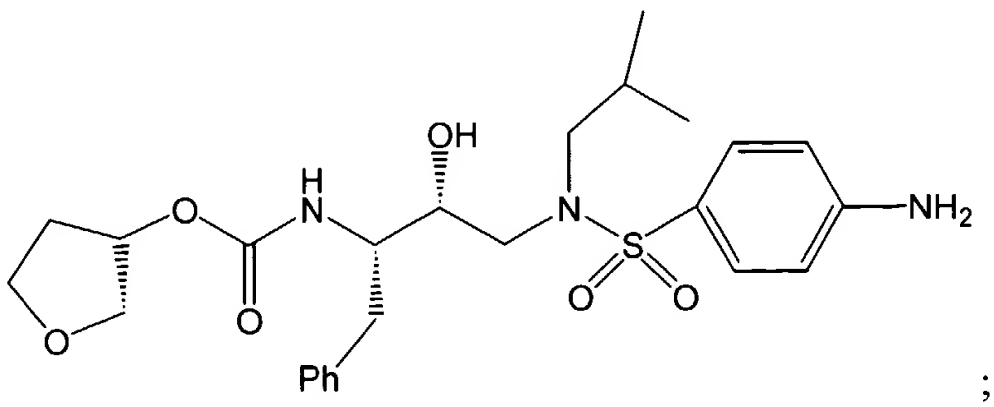
N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide ( saquinavir );

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1 -Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)- 3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

[1S-[1R-(R-),2S*])-N[1] [3-[[[(1,1 -dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1 -(phenylmethyl)propyl]-2-[(2quinolinylcarbonyl)amino]-butanediamide;



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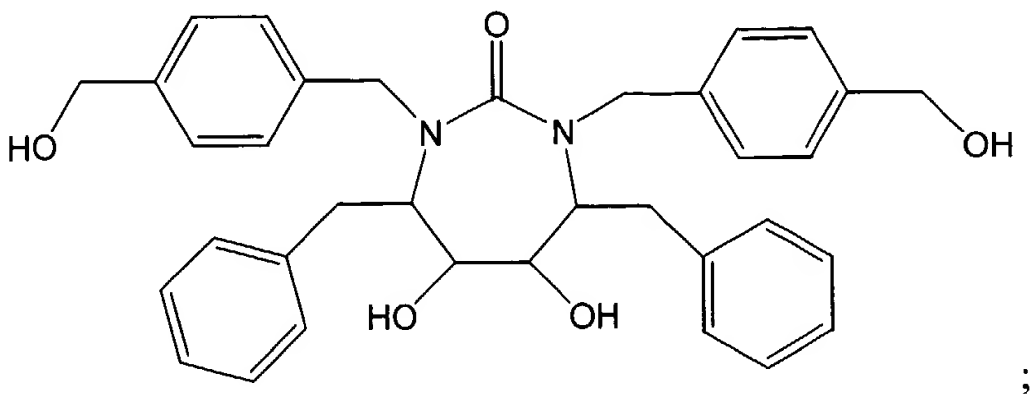
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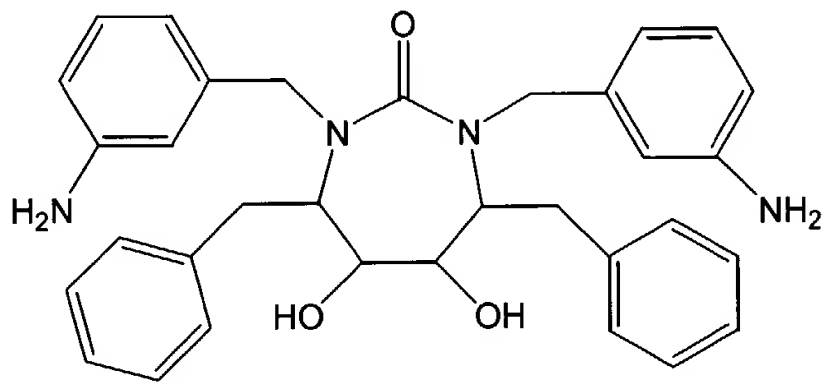
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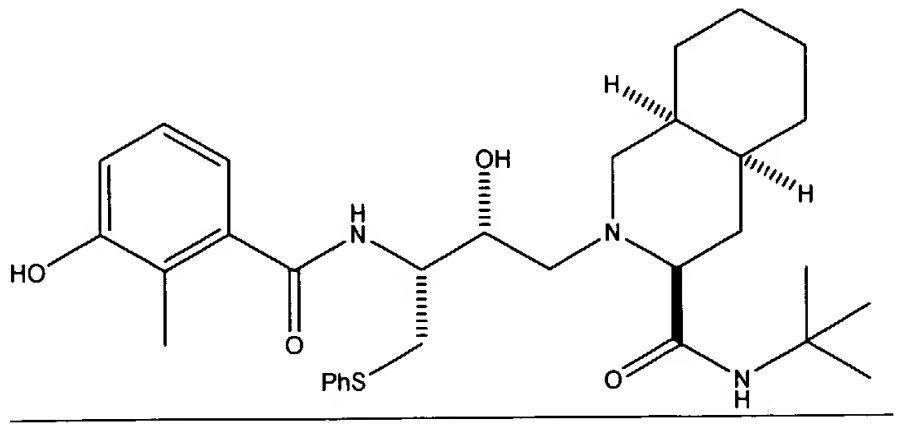
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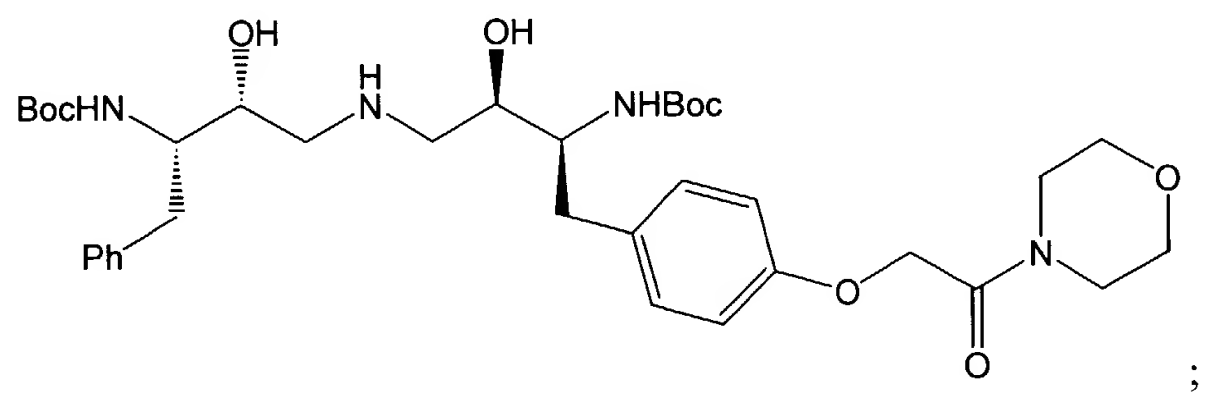
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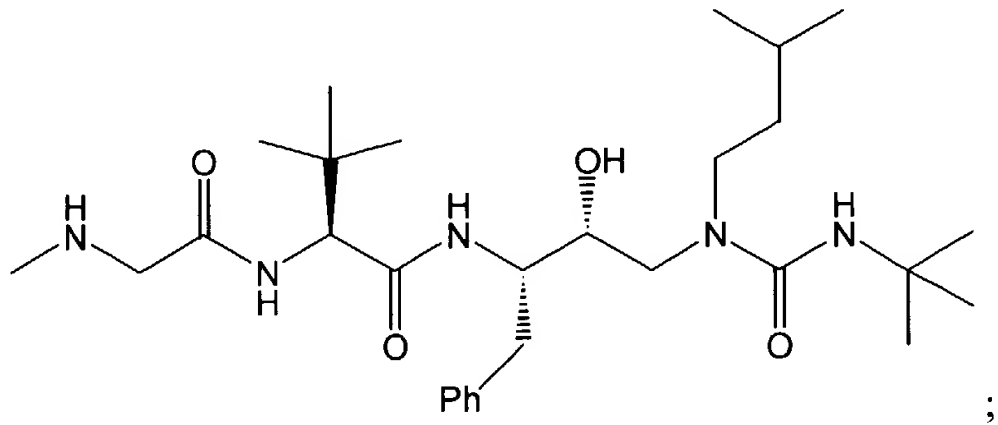

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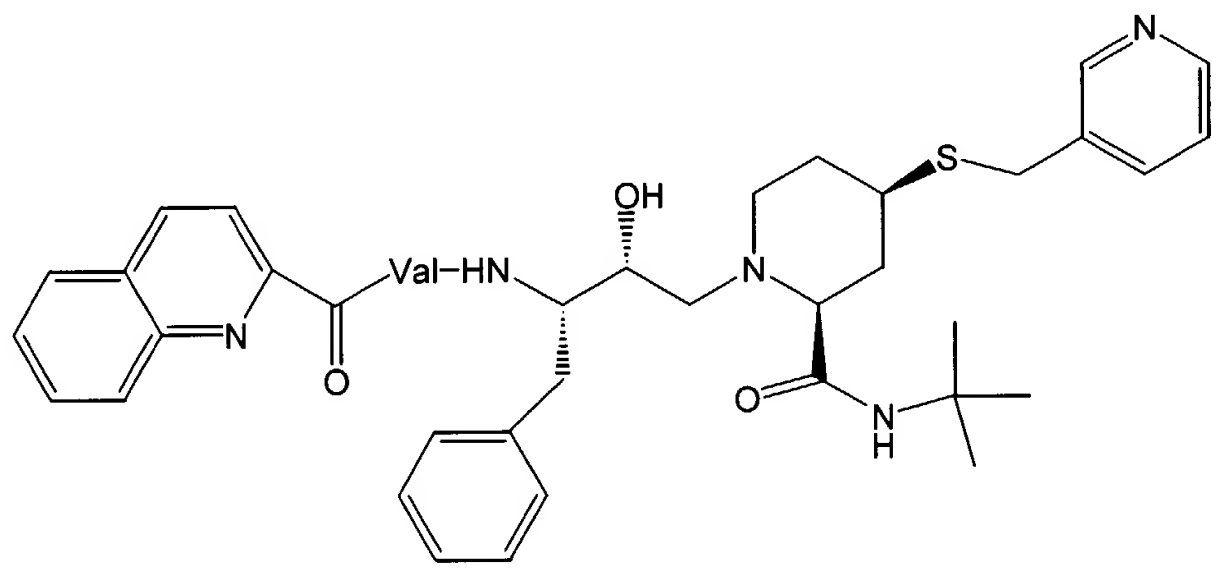

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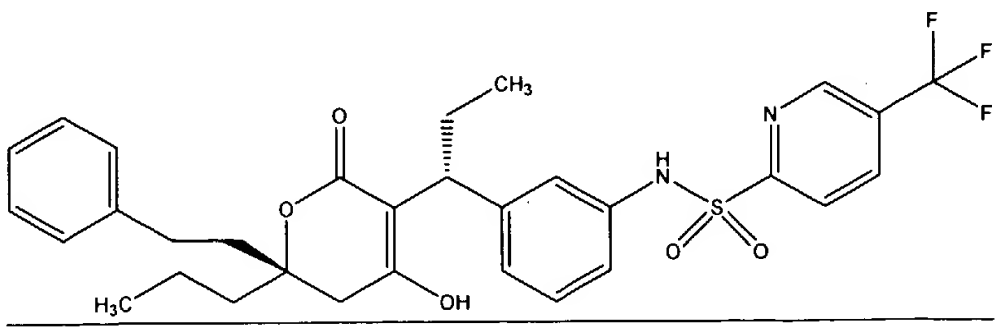


[tipranavir] ;

or a pharmaceutically acceptable salt thereof.

8. (once amended) The composition of Claim 1 wherein the solvent comprises (1) a pharmaceutically acceptable long chain fatty acid in an [the] amount of from about 40 [%] to about 75 weight % of the composition [by weight of the total solution]; (2) ethanol or propylene glycol in an [the] amount of from about 3 [%] to about 12 weight % of the composition [by

weight of the total solution]; and (3) water in an [the] amount of from about 0.4 [%] to about 1.5 weight % of the composition [by weight of the total solution].

9. (once amended) The composition of Claim 1 wherein the solvent comprises (1) oleic acid in an [the] amount of from about 40 [%] to about 75 weight % of the composition [by weight of the total solution]; (2) ethanol or propylene glycol in an [the] amount of from about 3 [%] to about 12 weight % of the composition [by weight of the total solution]; and (3) water in an [the] amount of from about 0.4 [%] to about 1.5 weight % of the composition [by weight of the total solution].

10. (twice amended) The composition of Claim 9 comprising (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) or a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) and another HIV protease inhibiting compound selected from the group consisting of:

(2S, 3S, 5S)-2-(2,6Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl]-amino-1,6-diphenylhexane;

N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ( indinavir );

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide ( saquinavir );

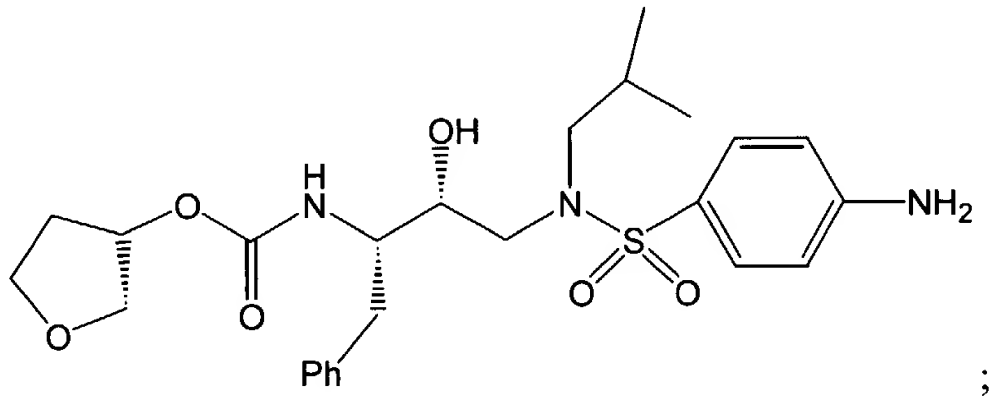
5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1 -Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)- 3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

[ [1S-[1R-(R-),2S*] )-N[1] [3-[[[(1,1 -dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1 -(phenylmethyl)propyl]-2-[(2quinolinylcarbonyl)amino]-butanediamide; ]

[1S-[1R-(R-),2S*] ]-N[1] [3-[[[(1,1 -dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1 -(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;



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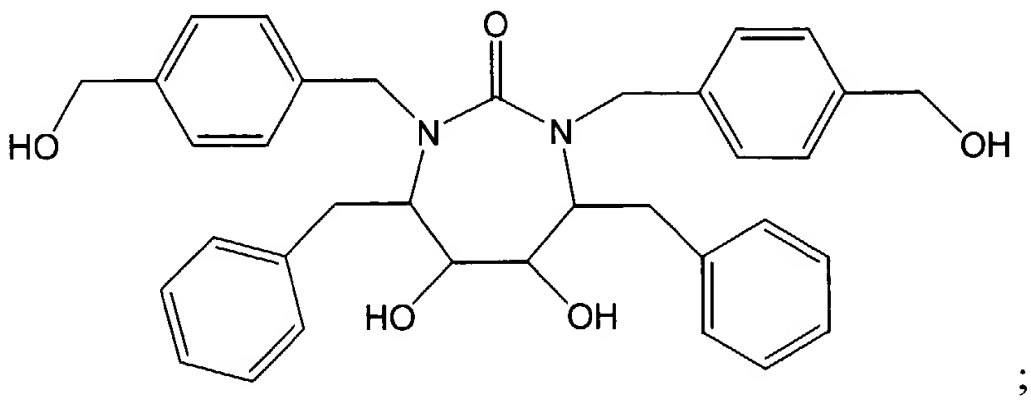

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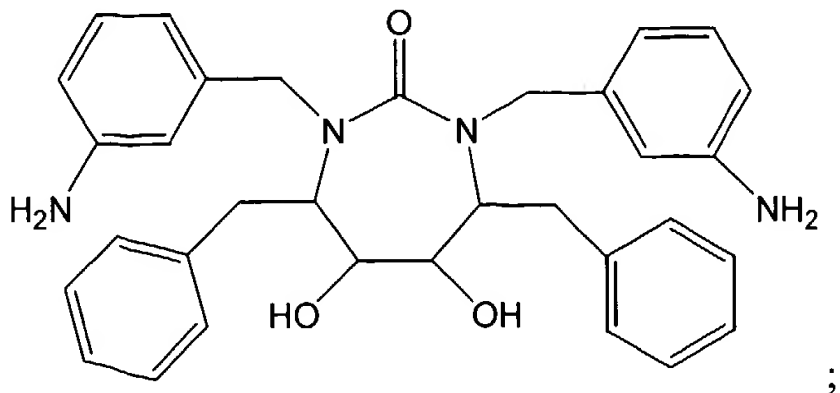
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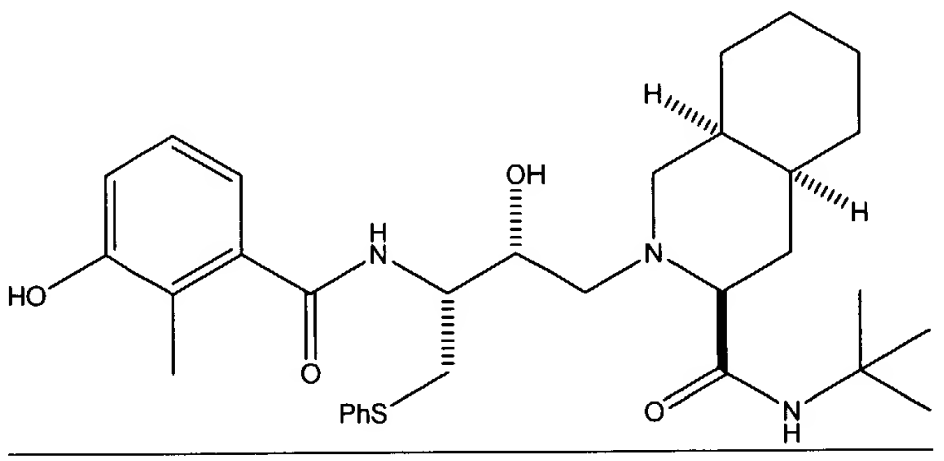
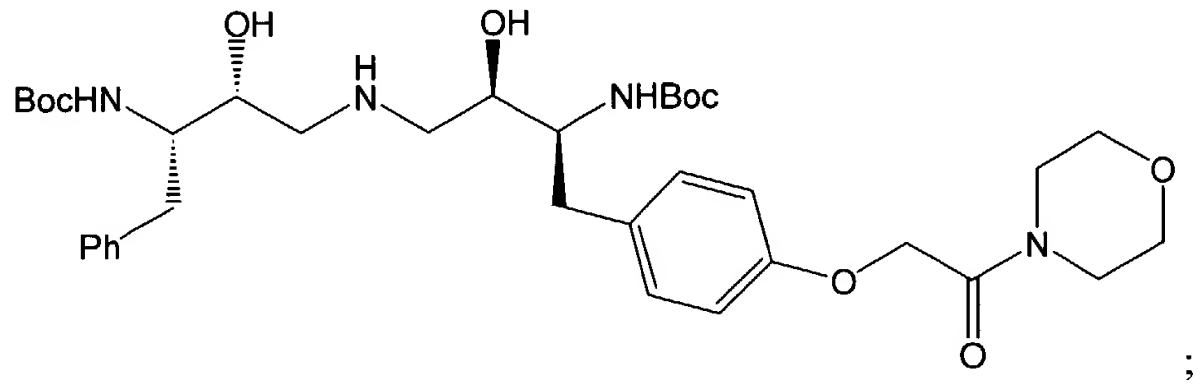
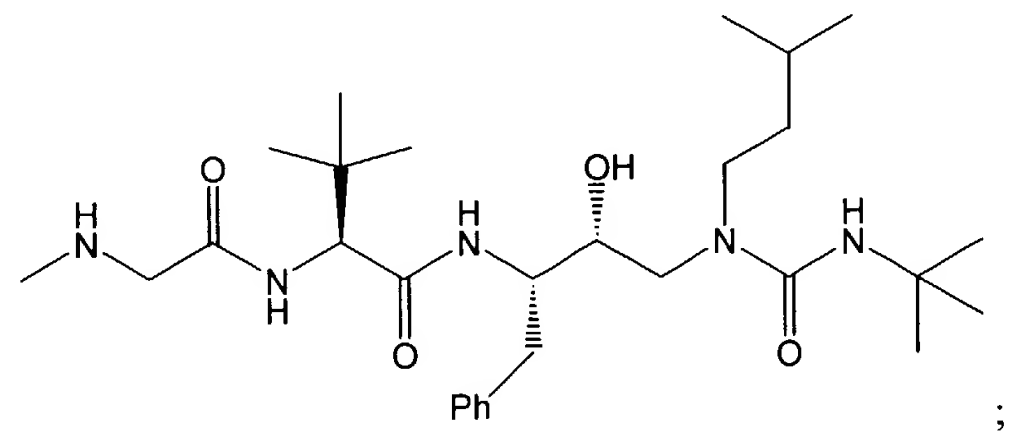
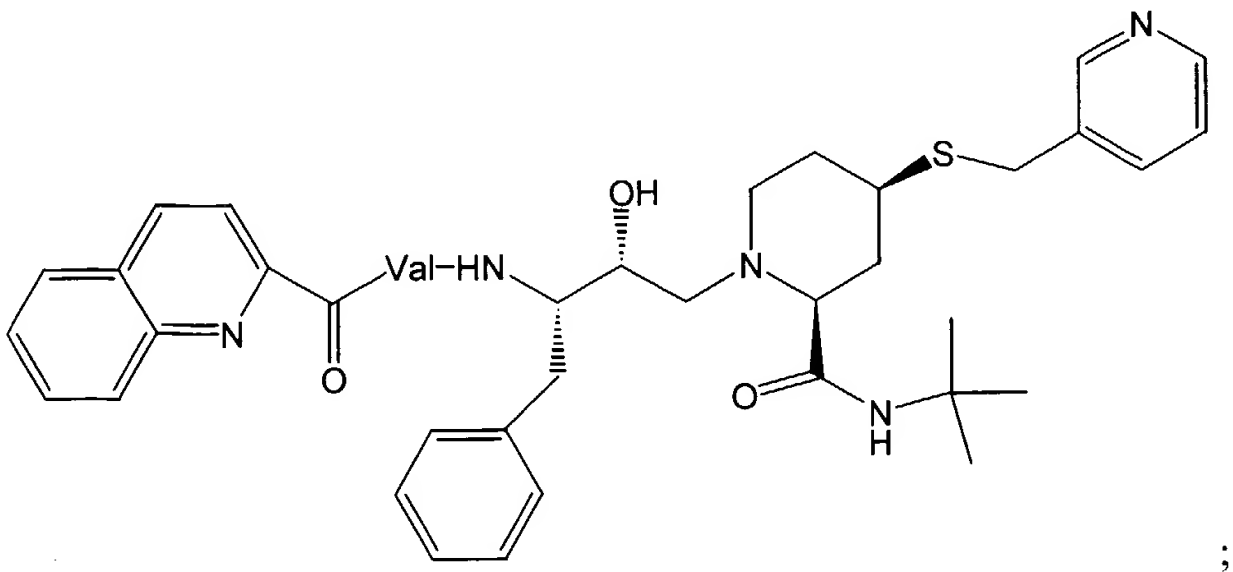
$H_2N$
$NH_2$
HO
OH
;

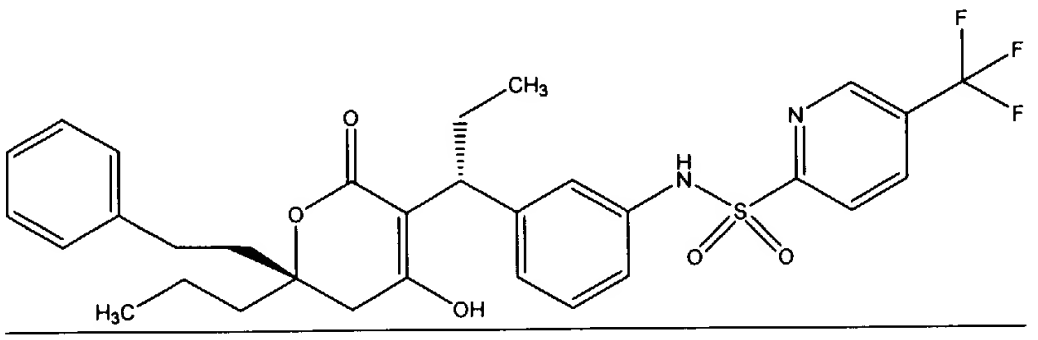

H
OH
H
N
N
HO
O
PhS
O
N
H
[ nelfinavir];


OH
OH
BocHN
H
N
NHBoc
Ph
O
O
N
O
;


O
OH
H
N
H
N
N
H
N
O
O
Ph
;




; and




[tipranavir] ;

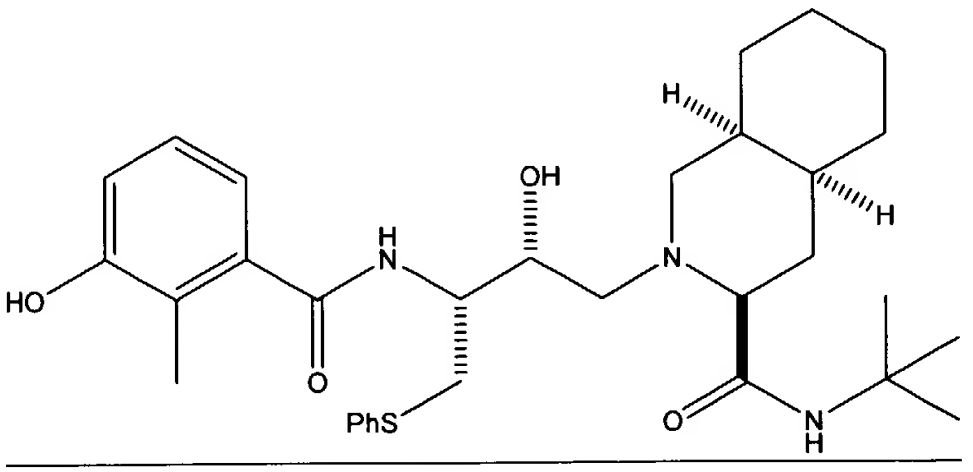
or a pharmaceutically acceptable salt thereof.

11. (twice amended) The composition of Claim 9 comprising (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) or a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) and another HIV protease inhibiting compound selected from the group consisting of:

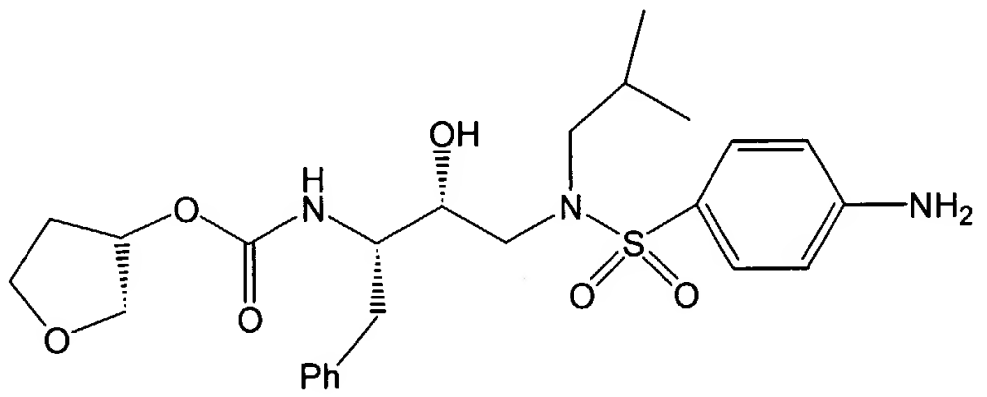
(2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3-hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyI-butanoyl)- amino-1,6-diphenylhexane,

N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ( indinavir ),

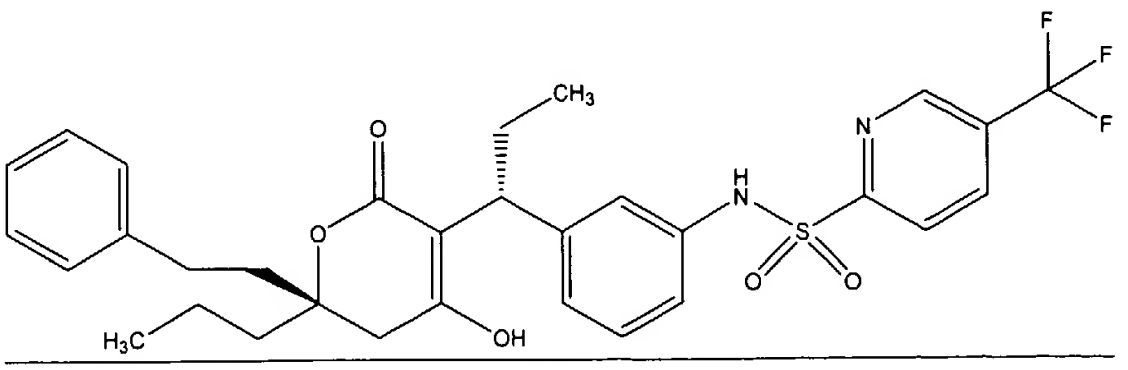
N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide ( saquinavir ),




( nelfinavir ),




and




( tipranavir );

or a pharmaceutically acceptable salt thereof.

14. (twice amended) The composition of Claim 1 which comprises:

(a) solubilized (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) in an [the] amount of from about 1 [%] to about 30 weight % of the composition [by weight of the total solution];

(b) a pharmaceutically acceptable organic solvent which comprises (1) [(i)] oleic acid in an [the] amount of from about 30 [%] to about 75 weight % of the composition [by weight of the total solution] and (2) ethanol in an [the] amount of from about 3 [%] to about 12 weight % of the composition [by weight of the total solution]; and

(c) water in an [the] amount of from about 0.4 [%] to about 3.5 weight % of the composition [by weight of the total solution]; and

(d) polyoxyl 35 castor oil in an [the] amount of from about 0 [%] to about 20 weight % of the composition [by weight of the total solution].

15. (twice amended) A pharmaceutical composition comprising:

(a) (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) in an [the] amount of about 10 weight % of the composition [by weight of the total solution,] ;

(b) a pharmaceutically acceptable organic solvent which comprises (1) oleic acid in an [the] amount of from about 70 [%] to about 75 weight % of the composition [by weight of the total solution]; and (2) ethanol in an [the] amount of from about 3 [%] to about 12 weight % of the composition [by weight of the total solution];

(c) water in an [the] amount of from about 0.4 [%] to about 1.5 weight % of the composition [by weight of the total solution]; and

(d) polyoxyl 35 castor oil in an [the] amount of about 6 weight % of the composition [by weight of the total solution].

17. (twice amended) The composition of Claim 1 which comprises:

(a) a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-

diphenyl-3-hydroxyhexane ( ritonavir ) and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyI butanoyl)- amino-1,6--diphenylhexane in an [the] amount of from about 1 [%] to about 45 weight % of the composition [by weight of the total solution];

(b) a pharmaceutically acceptable organic solvent which comprises (1) [(i)] oleic acid in an [the] amount of from about 30 [%] to about 75 weight % of the composition [by weight of the total solution] and (2) propylene glycol in an [the] amount of from about 1 [%] to about 15 weight % of the composition [by weight of the total solution]; and

(c) water in an [the] amount of from about 0.4 [%] to about 3.5 weight % of the composition [by weight of the total solution].

18. (twice amended) The composition of Claim 17 which comprises:

(a) a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyI butanoyl) amino-1,6-diphenylhexane in an [the] amount of from about 1 [%] to about 45 weight % of the composition [by weight of the total solution,] ;

(b) a pharmaceutically acceptable organic solvent which comprises (1) oleic acid in an [the] amount of from about 70 [%] to about 75 weight % of the composition [by weight of the total solution]; and (2) propylene glycol in an [the] amount of from about 1 [%] about 8 weight % of the composition [by weight of the total solution];

(c) water in an [the] amount of from about 0.4 [%] to about 1.5 weight % of the composition [by weight of the total solution]; and

(d) polyoxyl 35 castor oil in an [the] amount of from about 2.5 [%] to about 10 weight % of the composition [by weight of the total solution].

20. (once amended) A pharmaceutical composition comprising:

(a) a combination of solubilized (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane ( ritonavir ) in an [the] amount of about 3.9 weight % of

the composition [by weight of the total solution] and (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl) amino-3hydroxy-5-(2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl) amino-1,6-diphenylhexane in an [the] amount of about 15.6 weight % of the composition [by weight of the total solution,] ;

(b) a pharmaceutically acceptable organic solvent which comprises (1) oleic acid in an [the] amount of about 70 weight % of the composition [by weight of the total solution]; and (2) propylene glycol in an [the] amount of about 7.5 weight % of the composition [by weight of the total solution];

(c) water in an [the] amount of about 0.5 weight % of the composition [by weight of the total solution]; and

(d) polyoxyl 35 castor oil in an [the] amount of about 2.5 weight % of the composition [by weight of the total solution].